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Transformation of Aromatic Ether- and Amine-Containing Pharmaceuticals during Chlorine Disinfection

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Many of the human pharmaceuticals detected in municipal wastewater effluent, surface water, and groundwater contain functional groups that could undergo transformation reactions during chlorine disinfection. To assess the potential importance of these reactions to the environmental fate of pharmaceuticals, the rate of transformation of a group of compounds was measured over a pH range of 5 - 10. Several of the pharmaceuticals reacted rapidly with free chlorine (i.e., $HOCl/OCl^-$) and would be expected to undergo transformation under the conditions typically encountered in many chlorine disinfection systems. For compounds containing aromatic ether functional groups, the rate of transformation was strongly affected by the other substituents on the ring. The amine-containing pharmaceuticals underwent a rapid reaction with hypochlorous acid to form chlorinated amines, which could be converted back into the parent compound by reaction with thiosulfate. In the absence of thiosulfate, the chlorinated amines slowly decomposed to form species that could not be converted back into the parent compound. The reaction rates of the pharmaceuticals with combined chlorine (i.e., chloramines) were significantly slower, and transformation of the compounds would not be expected under the conditions encountered during chloramination.

Introduction

A variety of pharmaceutical compounds have been detected in municipal wastewater effluent and surface waters that receive inputs from wastewater treatment plants (*1* - *10*). In the United States, municipal wastewater effluent often is disinfected with chlorine prior to discharge. Chlorine also is used frequently as a primary or residual disinfectant during drinking water treatment. To better understand the potential for the transformation of pharmaceuticals during chlorine disinfection, it is necessary to quantify the kinetics of these reactions under conditions encountered in water and wastewater treatment systems.

When chlorine is used to disinfect denitrified wastewater effluent or drinking water, the active forms of the disinfectant are hypochlorous acid (HOCl) and hypochlorite (OCl^-), otherwise known as free chlorine. In addition to their biocidal properties, $HOCl/OCl^-$ species act as oxidants or as electrophiles, reacting selectively with certain functional groups on organic compounds. One of the best characterized reactions of $HOCl/OCl^-$ is the reaction of HOCl with phenols (*11* - *15*). In this reaction, HOCl reacts with the phenolate anion to yield mostly ortho- and para-substituted chlorophenols. As a result of the dissociable protons on both reactive species, the observed rate of reaction usually exhibits a maximum between the pK_a of HOCl (i.e., 7.5) and that of the phenol. Another well-characterized reaction of chlorine involves chlorine addition to primary and secondary amines (*16* - *19*). The reactive species in this reaction are the unprotonated amine and HOCl. As a result, the observed reaction rate typically exhibits a maximum between the pK_a of HOCl and the pK_a of the amine. The *N*-chlorocompounds formed by this reaction can be converted back to the parent compound by reactions with strong nucleophiles, such as thiosulfate or bisulfite, which are used to dechlorinate wastewater prior to discharge. In the absence of a strong nucleophile, the chlorinated amines can decompose to form stable products (*19* - *21*).

When chlorine is used to disinfect wastewater effluent that contains ammonia and organic nitrogen, most of the chlorine is converted into chloramines, which also are referred to as combined chlorine. Under typical conditions, most of the chloramines consist of monochloramine (i.e., NH_2Cl) along with lower concentrations of dichloramine and chlorine-substituted amines (*22*). In addition, many drinking water plants have begun using combined chlorine as their method of disinfection to reduce the formation of disinfection byproducts, such as trihalomethanes. Though chloramines are much weaker oxidants than $HOCl/OCl^-$, they also can react with some organic and nitrogenous compounds (*15*, *16*).

Previous observations indicate that certain pharmaceuticals react with chlorine (*23*). However, neither the functional groups responsible for this reaction nor the kinetics have been studied in detail. To gain insight into the types of functional groups that are transformed during chlorine disinfection, the reactions of $HOCl/OCl^-$ and monochloramine with pharmaceuticals that contain phenolic, amine and/or aromatic ether functional groups and several model compounds were studied over the range of pH values encountered in the aquatic environment.

Materials and Methods

The kinetics of chlorine reactions with 10 different pharmaceuticals was studied (Figure 1). These pharmaceuticals included five analgesics (acetaminophen, ibuprofen, indometacine, ketoprofen, and naproxen), four â-blockers (atenolol, metoprolol, nadolol, and propranolol), and one cholesterol-lowering compound (gemfibrozil). All 10 compounds and 6 model compounds were purchased from Sigma-Aldrich. These compounds and the other reagents used in these experiments were purchased at the highest available purity. Distilled water treated with a Barnstead Nanopure II system was used in all solutions and reagents.

New stock solutions of chlorine and monochloramine were prepared daily. The stock solution of NaOCl (↑ 14 mM) was prepared from a concentrated stock (↑ 5%) obtained from Fisher Scientific. The stock solution of monochloramine was prepared by adding concentrated NaOCl dropwise to a solution of ammonium chloride (12 mM) in a 1.2:1 ratio of ammonium to chlorine. The pH of the stock solution of monochloramine was 8.6. The total concentration of chlorine in each of these solutions was standardized in triplicate each day using iodometric titration (*24*).

The kinetics experiments were performed by adding an excess of chlorine or monochloramine (30:1 ratio of chlorine

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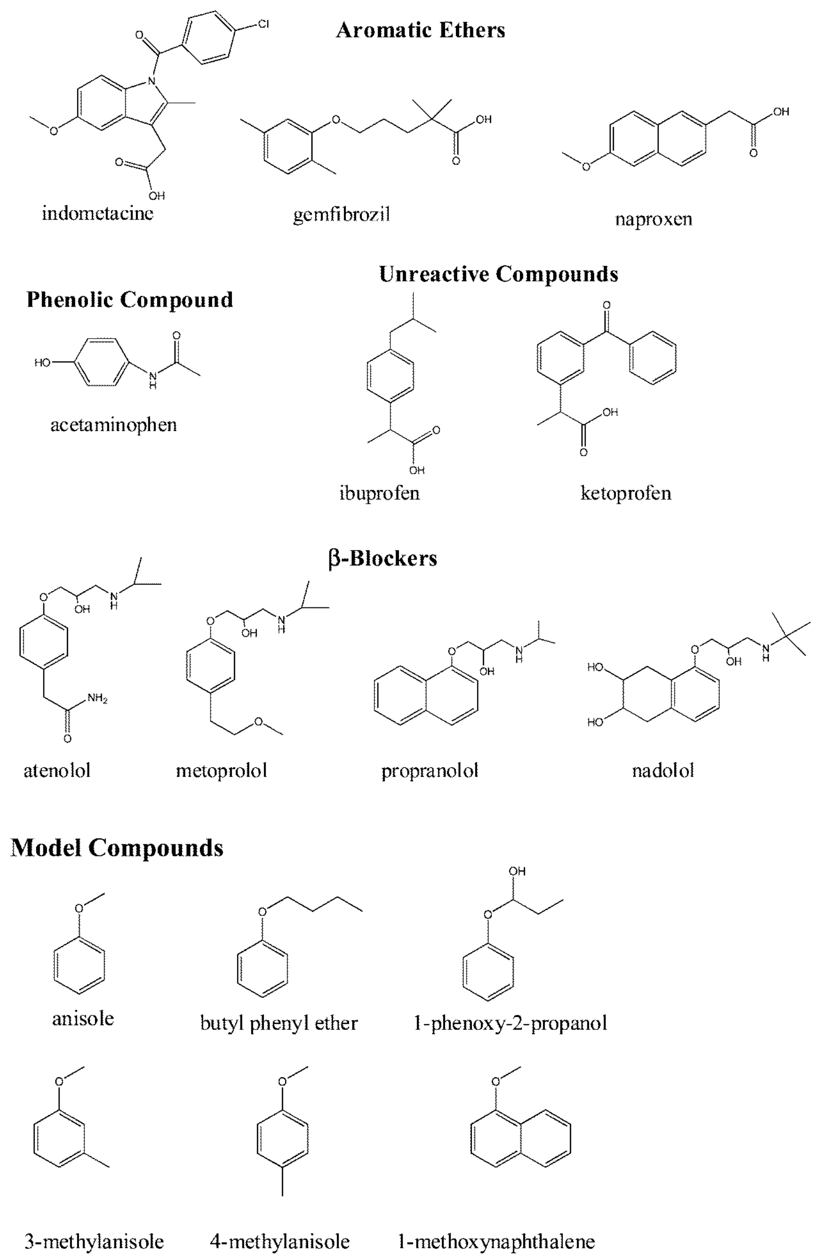


FIGURE 1. Structures of the compounds studied.

to pharmaceutical on a molar basis) to a solution of one of the pharmaceuticals (typical initial concentration 10 - 20 íM) and monitoring the disappearance of the pharmaceutical over time. The reactions were carried out in glass vials at room temperature (23 (2 °C). Prior to the experiments, the vials were soaked in a solution of NaOCl (↑ 20 mM). The reactions were conducted in the presence of 100 mM sodium nitrate electrolyte and 20 mM buffer. Borate buffer was used for pH values above 8.0 and phosphate buffer was used for pH values below 8.0. The pH of the reaction mixtures was measured using a pH meter at the start and end of each experiment. The measured pH never varied by more than 0.1 during the course of the experiment.

At evenly spaced time intervals, 1 mL aliquots of the reaction mixture were removed. The remaining chlorine was quenched by adding 100 íL of 0.1 M sodium thiosulfate. To minimize hydrolysis, the pH of the acidic solutions (pH < 6.5) was raised by adding 100 íL of 0.05 M NaOH. For experiments conducted with indometacine at a pH above 9.0, the pH was lowered by adding 20 íL of a 1 M solution of nitric acid after addition of thiosulfate because significant losses were observed in control experiments conducted at pH values above 9.0. The reactions of all 10 compounds were followed for at least 2 half-lives, up to a total of 5 days. For compounds that reacted too slowly to have completed 2 half-lives, the rates were estimated from the available data. These data are represented in the figures with hollow symbols.

Control solutions of pharmaceuticals without chlorine were run in parallel to the reactions for all pH values studied. In addition, the total concentration of chlorine was measured in control solutions containing only chlorine, electrolyte, and buffer using the DPD colorimetric method (*24*) for the whole pH range considered over a period of 5 days to verify that the concentration of chlorine remained constant.

The concentration of pharmaceuticals was measured using a Gynkotec high-performance liquid chromatography (HPLC) system with a UVD 170S UV detector. A C18 column (Altima C18LL) was used as the stationary phase with acetonitrile/formate buffer (25 mM, pH 3.4) as the eluent at a flow rate of 1 mL/min. The chromatographic conditions used for each compound are summarized in Table 1.

TABLE 1. HPLC Methods for Detection of Pharmaceuticals and Model Compounds

compd	% acetonitrile	% buffer	retention time (min)	wavelength (nm)
	Formate Buffer			
acetaminophen	20	80	5.6	260
atenolol	15	85	5.4	275
gemfibrozil	70	30	7.5	275
ibuprofen	70	30	6.2	230
indometacine	70	30	6.0	275
ketoprofen	70	30	4.8	250
metoprolol	30	70	6.3	225
nadolol	20	80	6.2	275
naproxen	70	30	4.9	275
propranolol	50	50	5.2	235
	HEPES Buffer			
anisole	70	30	5.6	275
butyl phenyl ether	70	30	9.0	275
1-methoxynaphthalene	70	30	7.6	275
3-methylanisole	70	30	6.3	275
4-methylanisole	70	30	6.2	275
1-phenoxy-2-propanol	70	30	4.3	275

The use of sodium thiosulfate to quench chlorine could convert *N*-chloro compounds back into their original form. Therefore, the reaction rates of the amine-containing pharmaceuticals with HOCl/OCl$^-$ also were measured without quenching the chlorine. In these experiments, the rates were measured by injecting the reaction solutions directly into the HPLC system at various times. Under these conditions, the reaction stopped shortly after injection into the HPLC system when the pharmaceutical and chlorine separated from each other. The eluent used in these experiments consisted of 30% HEPES buffer in deionized water (25 mM, pH 7.4) and 70% acetonitrile. The high-pH buffer was used in these experiments to minimize the formation of more reactive species at low pH. These steps were merited because the use of pH 3.4 formate buffer resulted in rapid reactions between chlorine and the pharmaceutical prior to separation.

Many of the pharmaceuticals studied contain an aromatic ether functional group. One compound with this functional group, anisole, has been shown to react with chlorine under strong chlorinating conditions, such as extremely low pH or in the presence of gaseous chlorine (*25*- *27*).

To further investigate the reactions of compounds with aromatic ether functional groups, the reaction of free chlorine with the model compounds depicted in Figure 1, anisole, butyl phenyl ether, 1-phenoxy-2-propanol, 3-methylanisole, 4-methylanisole, and 1-methoxynaphthalene (Sigma-Aldrich), was studied over a pH range of 5 - 10 in the manner described previously. The reactions were stopped by either directly injecting the sample into the HPLC or quenching the excess chlorine with thiosulfate. Both anisole and butyl phenyl ether are very volatile, and it was necessary to minimize headspace and to use airtight vials for the HPLC analysis. The compounds were analyzed by HPLC using the HEPES/acetonitrile method described above. The chromatographic conditions used for each compound are given in Table 1.

Results

All of the compounds studied were transformed by free chlorine except for ibuprofen and ketoprofen, which did not show any significant losses after a reaction time of 5 days. The remaining compounds all exhibited pseudo-first-order kinetics over at least 2 half-lives, with r^2 values greater than 0.98 for simple linear regressions of the logarithm of the pharmaceutical as a function of time. No loss of pharmaceuticals or free chlorine was observed in any of the controls.

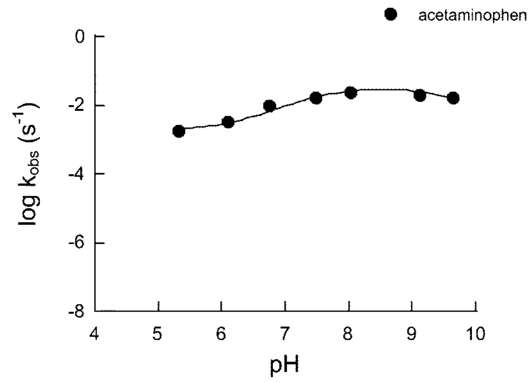


FIGURE 2. Reaction of acetaminophen with chlorine (HOCl, OCl$^-$). [pharmaceutical]$_i$) 20 íM, [HOCl]$_T$) 600 íM, [NaNO$_3$]) 100 mM, and [buffer]) 20 mM. The line represents the fitted model.

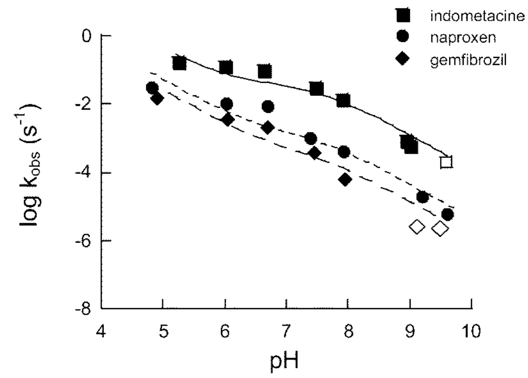


FIGURE 3. Reaction rates of gemfibrozil, indometacine, and naproxen with chlorine (HOCl, OCl$^-$). [pharmaceutical]$_i$) 10 íM, [HOCl]$_T$) 300 íM, [NaNO$_3$]) 100 mM, and [buffer]) 20 mM. The lines represent the fitted model. The hollow symbols represent estimated rate constants for compounds that did not undergo 2 half-lives.

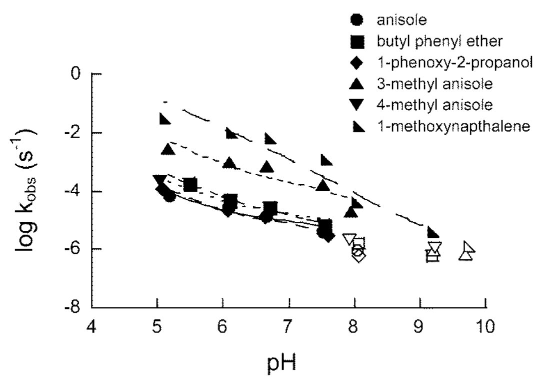


FIGURE 4. Reaction rates of model compounds with chlorine (HOCl, OCl$^-$). [pharmaceutical]$_i$) 20 íM, [HOCl]$_T$) 600 íM, [NaNO$_3$]) 100 mM, and [buffer]) 20 mM. The lines represent the fitted model. The hollow symbols represent estimated rate constants for compounds that did not undergo 2 half-lives.

The observed rate of transformation of the pharmaceuticals and model compounds with free chlorine varied as much as 5 orders of magnitude between pH 5 and pH 10 (Figures 2 - 5). The reaction rates usually increased as the pH decreased from 10 to 7 because HOCl is significantly more reactive than OCl$^-$. In several cases, the reaction rates continued to increase below pH 7, indicating that the pH effect at low pH values is due to more than just the protonation of OCl$^-$.

When solutions of the amine-containing compounds (i.e., â-blockers) were injected into the HPLC system 2 min after addition of an excess of chlorine, a new compound was

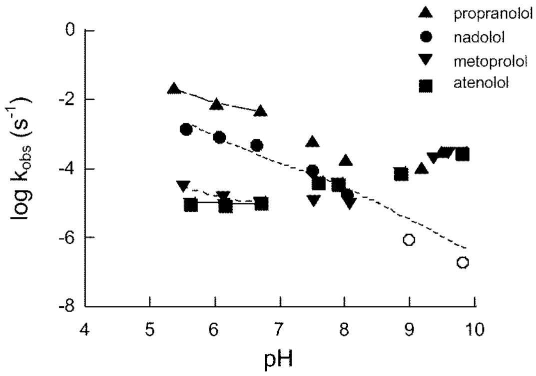


FIGURE 5. Reaction rates of â-blockers with chlorine (HOCl, OCl⁻). [pharmaceutical]$_i$) 20 íM, [HOCl]$_T$) 600 íM, [NaNO$_3$]) 100 mM, and [buffer]) 20 mM. The lines represent the fitted model. The hollow symbols represent estimated rate constants for compounds that did not undergo 2 half-lives.

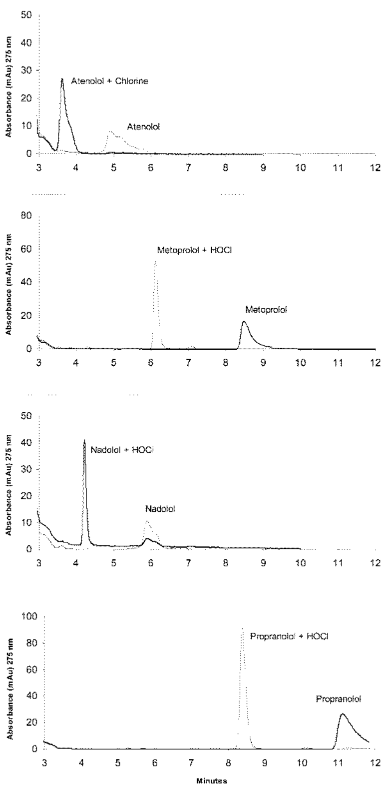


FIGURE 6. Chromatograms showing the formation of an N-chloro compound from the â-blockers (20 íM HOCl, 20 íM pharmaceutical, pH 8, t) 2 min).

observed that eluted prior to the unchlorinated parent compound (Figure 6). The rapid transformation of these compounds was not observed when the chlorine was quenched prior to HPLC analysis (Figure 5), indicating that the product was converted back to its initial form when thiosulfate was added.

The rate of reaction of the compounds with combined chlorine was usually much slower than that observed in the presence of free chlorine (Figure 7). In addition, the reaction of the pharmaceuticals with monochloramine did not always exhibit good first-order kinetics. The r^2 values for the regressions were often below 0.98, though in no case was the value below 0.95. The deviation from first-order kinetics was caused by changes in both the total concentration of chlorine and the form of the chlorine over the time period of the reactions (5 days) for the solutions having a pH value of less than 8. At low pH values, monochloramine is converted to other species (i.e., dichloramine and trichloramine) (*28*), which vary in their reactivity with organic compounds.

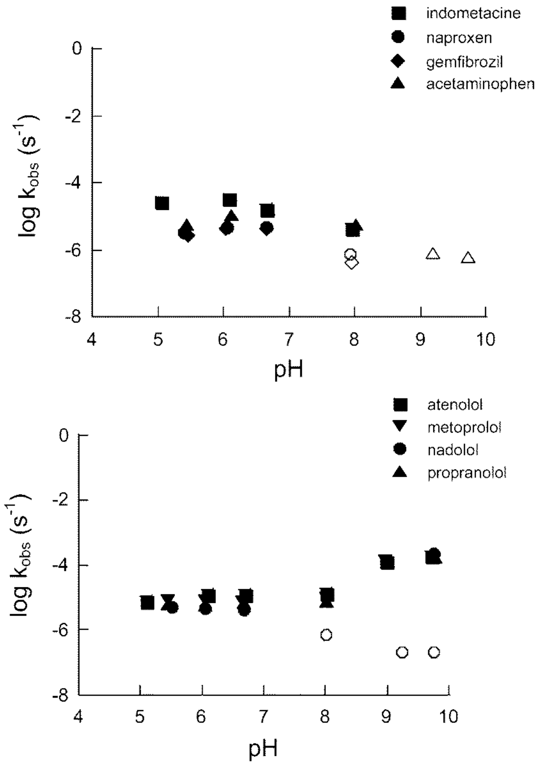


FIGURE 7. Reaction rates of pharmaceuticals with combined chlorine. For acetaminophen, atenolol, metoprolol, nadolol, and propranolol, [pharmaceutical]$_i$) 20 íM, [combined chlorine]$_{T,i}$) 600 íM, [NaNO$_3$]) 100 mM, and [buffer]) 20 mM. For gemfibrozil, indometacine, and naproxen, [pharmaceutical]$_i$) 10 íM, [combined chlorine]$_{T,i}$) 300 íM, [NaNO$_3$]) 100 mM, and [buffer]) 20 mM. The hollow symbols represent estimated rate constants for compounds that did not undergo 2 half-lives.

Discussion

Reaction of Acetaminophen with Free Chlorine. Acetaminophen contains a phenolic functional group as well as an amide. Amides do not react rapidly with free chlorine (*29*), so the main site of the reaction is most likely the phenol. The reaction rates for acetaminophen followed the expected behavior for a substituted phenol undergoing chlorine addition to the aromatic ring. The rate constants for acetaminophen were estimated by considering the following reactions:

$$HOCl + ROH \xrightarrow{k_1} products \tag{1}$$

$$HOCl + RO^- \xrightarrow{k_2} products \tag{2}$$

where ROH is the protonated form of acetaminophen and RO^- is the phenolate form. The reaction of OCl^- was not considered in this model because previous research (*11*-*15*) has shown that hypochlorite does not react at a significant rate with substituted phenols. The values for the second-order rate constants were calculated from the pseudo-first-order rate constants by dividing the k_{obs} values by the total concentration of chlorine. The two rate constants in eqs 1 and 2 (Table 2) were then calculated from the second-order rate constants by minimizing the sum of the squares of the difference between the logarithm of the measured k and that of the predicted k, as depicted by the solid line in Figure 2.

TABLE 2. Rate Constants for the Reaction of Pharmaceuticals and Model Compounds with Chlorine

	k_1 ($M^{-1}s^{-1}$)	k_2 ($M^{-1}s^{-1}$)	k_3 ($M^{-1}s^{-1}$)	k_{H^+} ($M^{-2}s^{-1}$)	k_{mono} ($M^{-1}s^{-1}$)	half-life (min), HOCl/OCl$^-$ [a]	half-life (min), monochloramine[a]
			Pharmaceuticals				
acetaminophen	3.1×10^{0}	7.0×10^{3}			$<1.3 \times 10^{-3}$	5.2×10^{0}	$>6.2 \times 10^{4}$
atenolol			1.7×10^{-2}	0.0×10^{0}	$<3.0 \times 10^{-2}$	6.3×10^{3}	$>2.7 \times 10^{3}$
gemfibrozil			7.3×10^{-1}	4.2×10^{6}	$<8.0 \times 10^{-4}$	9.3×10^{1}	$>1.0 \times 10^{5}$
indometacine			6.7×10^{1}	6.9×10^{7}	$<1.5 \times 10^{-2}$	1.4×10^{0}	$>5.4 \times 10^{3}$
metoprolol			1.7×10^{-2}	1.1×10^{4}	$<3.0 \times 10^{-2}$	5.9×10^{3}	$>2.7 \times 10^{3}$
nadolol			1.8×10^{-1}	1.3×10^{6}	$<4.0 \times 10^{-4}$	3.4×10^{2}	$>2.0 \times 10^{5}$
naproxen			2.4×10^{0}	8.7×10^{6}	$<8.0 \times 10^{-4}$	3.3×10^{1}	$>1.0 \times 10^{5}$
propranolol			7.5×10^{0}	6.6×10^{6}	$<3.0 \times 10^{-2}$	1.3×10^{1}	$>2.7 \times 10^{3}$
			Model Compounds				
anisole			1.9×10^{-2}	1.9×10^{4}			
butyl phenyl ether			2.5×10^{-2}	8.2×10^{4}			
1-methoxynaphthalene			3.5×10^{-1}	2.4×10^{7}			
3-methylanisole			3.3×10^{-1}	1.2×10^{6}			
4-methylanisole			3.2×10^{-2}	4.7×10^{4}			
1-phenoxy-2-propanol			1.4×10^{-2}	2.5×10^{4}			

[a] The half-lives were calculated assuming a total chlorine concentration of 10 mg/L and a pH value of 7.

The fact that k_2 is much larger than k_1 is consistent with the phenolate form of the compound adding more electron density to the aromatic ring. Using the correlation between the Hammett substituent constants and k_2 developed by Gallard and von Gunten (*14*), the estimated value of k_2 for acetaminophen is 14000 $M^{-1}s^{-1}$ assuming a value of 0.00 for σ_p for the amide substituent (*30*). This discrepancy between this estimated value and the measured value (i.e., 7000 $M^{-1}s^{-1}$) value is reasonable considering the uncertainty of the experimental values of the correlation and the measurements for acetaminophen.

Reaction of Gemfibrozil, Indometacine, and Naproxen with Free Chlorine. The reaction rates of the aromatic ethers gemfibrozil, indometacine, and naproxen all increased as pH decreased (Figure 3). The reaction of chlorine with these compounds was modeled as an attack of HOCl on the aromatic ring. To account for the increased reaction rate below the pK_a of HOCl, both a neutral and an acid-catalyzed reaction were considered:

$$HOCl + compound \xrightarrow{k_3} products \qquad (3)$$

$$H^+ + HOCl + compound \xrightarrow{k_{H^+}} products \qquad (4)$$

The protonation of the carboxylate group was not considered because it would have little effect on the electron density of the aromatic ring due to its distance from the ring. Although alternative explanations, such as the existence of trace concentrations of Cl_2 and other reactive species (*22*), could be invoked to explain the increased reaction rate at low pH, the acid-catalyzed mechanism was chosen to maintain consistency with previous studies in which similar behavior was observed (*13, 14*). As seen in Figure 3, the model does not fit the data as well at low pH values, indicating that the other mechanisms also may be involved.

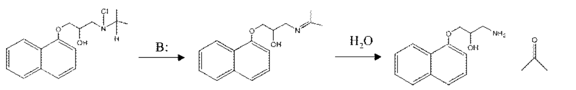
Reaction of Model Compounds with Chlorine. To assess the reactivity of aromatic ethers with structures similar to those compounds depicted in Figure 3 without the confounding effects of other functional groups, a series of model compounds was studied (Figure 4). The pH dependence of the reaction rate of these model compounds was similar to the dependence observed for the pharmaceuticals depicted in Figure 3. Furthermore, the rate constants for reactions 3 and 4 were similar to those observed for the pharmaceuticals (Table 2). It should be noted that some of the high-pH data were excluded from the calculation of the rate constants in Table 2 because the reactions did not complete 2 half-lives after 5 days. As was the case for the pharmaceuticals, the model does not always fit the data well at low pH values.

The reaction rate of the unsubstituted compounds (i.e., anisole, butyl phenyl ether, 1-phenoxy-2-propanol) was slower than the reaction rate for the pharmaceuticals by several orders of magnitude. This indicates that although the ether group does add electron density and activates the ring for reaction, it is not the only factor causing the pharmaceuticals to react with chlorine.

The reaction rate of the substituted anisole with a substituent in the para position (i.e., 4-methylanisole) was as slow as that of the unsubstituted anisoles. However, the substituted anisoles with a substituent in the meta position (i.e., 3-methylanisole) or with rings occupying the meta and para positions (i.e., 1-methoxynaphthalene) exhibited faster kinetics. The faster kinetics of the meta-substituted compounds relative to the unsubstituted or the para-substituted compounds is consistent with the electron-donating properties of the substituents to the electron density of the ring and, in the case of the ortho and para substituents, resonance delocalization of the electrons. Because ring substituents can add electron density to the positions that are ortho or para to it, a meta-substituted anisole results in the ortho and para positions having added electron density from both the ether functional group and the other substituent. The sites with the higher electron density are presumably more susceptible to electrophilic attack by chlorine.

Reaction of β-Blockers with Free Chlorine. The β-blockers all exhibited a strong dependence of reactivity on pH (Figure 5). All four of the compounds exhibited an increase in reaction rates below pH 7, and three of the compounds (i.e., atenolol, metoprolol, and propranolol) showed an increased reaction rate above pH 8. The relative reactivity of the compounds at pH values below 7 was consistent with the trends observed for the substituted anisoles. Those compounds that contained substituents in the meta position (i.e., propranolol and nadolol) reacted faster than those with substituents in the para position (i.e., metoprolol and atenolol). As was the case with the substituted anisoles, this phenomenon is most likely related to a combination of electron donation by the substituents and resonance delocalization by the para substituents.

In addition to the aromatic ether functional group, the β-blockers also contain an amine group, which is known to readily undergo chlorine addition. The three compounds that exhibited an increase in reactivity at pH values above 8 (i.e., atenolol, metoprolol, and propranolol) all contain a secondary amine with a secondary propyl substituent. The â-blocker that does not exhibit an increase in reactivity at pH values above 8 (i.e., nadolol) contains a *tert*-butyl group. The difference in reactivity associated with this slight change in molecular structure is most likely attributable to the presence of an R hydrogen in atenolol, metoprolol, and propranolol. Chloramines that have hydrogen on the carbon R to the amine have been shown to undergo a base-catalyzed decomposition reaction in which the hydrogen is abstracted and an imide is formed. The imide then hydrolyzes, causing cleavage of the bond between the nitrogen and carbon and removal of the R carbon and its substituents (*19*, *20*). An example of how this reaction would occur for propranolol can be seen in eq 5.


(5)

The first step of this reaction, the formation of the *N*-chloro compound, is typically rapid and is a function of the basicity of the amine. Using the correlation described by Margerum et al. (*16*) and the reported values for the pK_a values for the secondary amines in the three â-blockers (9.5 - 9.7) (*31*, *32*), the half-life for the formation of the *N*-chloro compound is less than 5 s over the whole pH range considered in these experiments. The second step in the reaction, the decomposition of the chloramine, is expected to be slower at the ionic strength and pH values considered in these experiments. When sodium thiosulfate is used to quench the chlorine, the *N*-chloro compounds are converted back to the parent compound, and as a result, the rate constants depicted in Figure 5 represent the decomposition of the chloramine.

To confirm the occurrence of the reactions described above, the samples were injected into the HPLC system before and after addition of free chlorine (Figure 6). For all four compounds, the retention time of the compound shifted immediately after addition of chlorine. The peak corresponding to the parent compound was completely transformed to the new peak when an excess of free chlorine was added, and a stoichiometry of one chlorine per â-blocker was observed. The products formed at pH 5 and 8 were relatively stable for all four â-blockers (less than 10% loss after 12 h). However, at pH 10, the new peak formed by chlorination of nadolol was stable, while the product formed from atenolol, metoprolol, and propranolol decayed rapidly with a half-life of approximately 30 min. The rate of this decay was independent of the concentration of chlorine initially present, which indicates that the rate-limiting step did not involve the initial attack of chlorine. In all four cases, the new compound could be converted back into the parent compound by addition of excess sodium thiosulfate. All of these observations were consistent with the formation of an *N*-chloro compound that underwent an irreversible conversion at high pH values.

The observed first-order transformation rates were used to estimate second-order rate constants for the compounds depicted in Figure 5 using the approach previously described for the other pharmaceuticals and the substituted anisoles. The rate constants for atenolol, metoprolol, and propranolol were calculated only on the basis of the data for pH values less than 7 because the mechanism of loss at high pH was not the same. Results of these calculations indicate values of k_3 and k_{H^+} varying by approximately 3 orders of magnitude, with higher rates for the meta-substituted compounds (Table 2).

Reaction of Pharmaceuticals with Combined Chlorine. The reaction rates observed when monochloramine was added to solutions of the pharmaceuticals were typically much slower than those observed with free chlorine (Figure 7). The observed transformation rates also exhibited a weaker pH dependence, with slightly faster rates observed at lower pH values for most of the compounds. This pH effect is likely attributable to the conversion of monochloramine to more reactive species, such as dichloramine.

The reaction rates of propranolol, metoprolol, and atenolol with combined chlorine at a pH greater than 9 were approximately the same as the reaction rates seen at those pH values with free chlorine. This indicates that the same mechanism of loss occurred with both forms of chlorine for these compounds at high pH values. As in the case of free chlorine, the loss of the compound is likely due to the chlorine-substituted compound undergoing base-catalyzed decomposition.

Rate constants for the reaction of the pharmaceuticals with monochloramine were estimated using an equation similar to that for the reactions with free chlorine (Table 2).

$$\text{monochloramine} + \text{pharmaceutical} \xrightarrow{k_{mono}} \text{products} \quad (6)$$

The reaction rates for the high pH values (>9) were used for these estimates when possible because of the loss of total chlorine and because the conversion of monochloramine to other species complicates the interpretation of the data at lower pH values. The use of high-pH data was not appropriate for four of the pharmaceuticals (indometacine, atenolol, metoprolol, and propranolol). In the case of indometacine, the compound completely hydrolyzed in the controls at high pH values, and in the case of the three â-blockers, the mechanism of loss involves decomposition of the chlorine-substituted amine at high pH values. The maximum k_{mono} values for these compounds were estimated from the reaction rates measured at pH values below 7. This likely resulted in an overestimation of the maximum value for the rate constant because of the presence of more reactive species at low pH. Irrespective of which data were used, all of these reactions were extremely slow and only a small amount of pharmaceutical had disappeared after 5 days. As a result, the rate constants calculated represent estimated maximum values.

Expected Transformation during Chlorination. During typical disinfection of wastewater effluent, the water receives a dose of chlorine that is approximately 10 mg/L (i.e., 0.14 mM total Cl[I]) for a contact time of around 60 min. At this concentration of chlorine and time, if the overall second-order rate constant for the reaction (i.e., $k_3 + k_{H^+}[H^+]$) were 0.2 $M^{-1}s^{-1}$, 90% of the pharmaceutical would be transformed during disinfection. This corresponds to a log k_{obs} value of approximately -4 under the conditions used in these experiments. Among the compounds tested, only indometacine, acetaminophen, and propranolol will be significantly transformed by free chlorine over the entire pH range studied. Naproxen and gemfibrozil will be significantly transformed during chlorination at pH values below 8, which is in the pH range typically encountered in water and wastewater treatment plants. Atenolol, nadolol, ketoprofen, and ibuprofen react too slowly in the pH range of natural waters to be significantly transformed during water treatment processes. None of the 10 compounds studied react rapidly enough with combined chlorine to be transformed during disinfection.

An unintentional result of switching from free to combined chlorine for water disinfection or forgoing nitrification in wastewater treatment is that there will be much less transformation of these and other pharmaceuticals during chlorine disinfection. This factor could be relevant to attempts to predict the loading of pharmaceuticals to receiving waters and the design of monitoring programs for pharmaceuticals. The biological activity of the transformation products is unknown, so the fact that the compounds are transformed by chlorine does not necessarily alleviate all concerns associated with their presence in the aquatic environment.

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